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Synthesis of 1-oxa-9-azaspiro[5.5]undecane-9-sulfonamides bearing a diverse molecular periphery and a rare zinc-binding group for carbonic anhydrase interrogation

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Contents

General

All commercial reagents and solvents were used without further purification, unless otherwise noted. THF for the synthesis was distilled over Na and stored under nitrogen over freshly activated molecular sieves 4 Å. The NMR spectra were recorded on a Bruker Avance III 400 spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; chemical shifts are reported as parts per million (δ, ppm)) (Bruker, Billerica, MA, USA); the residual solvent peaks were used as internal standards: 7.28 and 2.50 ppm for ^{1}H in $CDCl_3$ and DMSO-*d*$_6$, respectively, 40.01 and 77.02 ppm for ^{13}C in DMSO-*d*$_6$ and $CDCl_3$, respectively. Mass spectra were recorded on a Bruker Maxis HRMS-ESI-qT spectrometer (ESI ionization) (Bruker, Billerica, MA, USA). The melting points were determined in open capillary tubes on a Stuart SMP30 Melting Point Apparatus (Staffordshire, UK). Analytical thin-layer chromatography was carried out on Silufol UV-254 silica gel plates (Chemapol, Czech Republic) using appropriate mixtures of ethyl acetate and hexane. The compounds were visualized with short-wavelength UV light. Column chromatography was performed on silica gel 60 (230–400 mesh).

General procedure for the synthesis of compounds 4a-j

To a solution of chlorosulfonyl isocyanate (0.14 g, 1 equiv., 1 mmol) in CH_2Cl_2 (10 ml) a solution of *tert*-butyl alcohol (0.1 g, 1.3 equiv., 1.3 mmol) in CH_2Cl_2 (1 ml) was added dropwise at 0 °C. The mixture was stirred at that temperature for 1 h and then treated with a solution of an amine hydrochloride **1a-j** (1 equiv., 1 mmol) and triethylamine (0.3 g, 3 equiv., 3 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred at room temperature overnight, diluted with water (25 ml) and the organic layer was separated. The aqueous layer was additionally extracted with CH_2Cl_2 (2 x 15 ml). The combined organic extracts were washed with 3% aqueous citric acid (2 x 15 ml), brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Brief fractionation over silica gel using 80:1 CH_2Cl_2/MeOH as an eluent. Fractions containing compounds **3** were pooled and concentrated *in vacuo*. The residue was taken up in 1,4-dioxane (1 mL), the solution was cooled to 0 °C and treated with 4M solution of HCl in 1,4-dioxane (1 ml). The resulting mixture was stirred at room temperature over 18 h and the volatiles were removed *in vacuo*. The residue was crystallized from anhydrous ethanol to give the title compound.

4-[(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)methyl]-1-oxa-9-azaspiro[5.5]undecane-9-sulfonamide (4a) Yield 100 mg, (28 %), white solid, m.p. 89-90 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 6.65 (s, 2H), 4.34 (t, *J* = 5.1 Hz, 1H), 3.63 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.56 – 3.37 (m, 1H), 3.22 – 3.03 (m, 2H), 2.85 (tt, *J* = 9.0, 4.6 Hz, 1H), 2.78 – 2.73 (m, 2H), 2.72 – 2.61 (m,

1H), 2.29 (t, *J* = 13.4 Hz, 1H), 2.22 – 2.14 (m, 1H), 2.13 – 2.02 (m, 1H), 1.62 – 1.42 (m, 4H), 1.31 (td, *J* = 14.0, 4.0 Hz, 1H), 1.24 – 1.09 (m, 1H), 1.08 – 1.01 (m, 3H), 0.91 – 0.81 (m, 2H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.39, 172.12, 68.72, 60.25, 41.59, 35.53, 32.93, 31.88, 28.78, 25.77, 7.87, 6.78; HRMS (ESI), m/z calcd for $C_{15}H_{25}N_4O_4S[M+H]^+$ 357.1591, found 357.1594.

4-{[3-(2-Methoxyethyl)-1,2,4-oxadiazol-5-yl]methyl}-1-oxa-9-azaspiro[5.5]undecane-9-sulfonamide (4b)

Yield 145 mg, (38 %), white solid, m.p. 74-75 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.65 (s, 2H), 3.72 – 3.61 (m, 3H), 3.52 (t, *J* = 11.5 Hz, 1H), 3.32 (s, 4H), 3.22 (s, 3H), 3.11 (dd, *J* = 26.9, 18.8 Hz, 2H), 2.91 (t, *J* = 6.3 Hz, 2H), 2.84 (dd, *J* = 17.0, 4.8 Hz, 3H), 2.67 (t, *J* = 10.8 Hz, 1H), 2.36 – 2.09 (m, 2H), 1.63 – 1.43 (m, 4H), 1.38 – 0.98 (m, 3H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.96, 168.02, 68.41, 68.20, 59.72, 57.81, 41.07, 38.83, 35.01, 32.37, 31.38, 28.26, 26.00, 25.24; HRMS (ESI), m/z calcd for $C_{15}H_{27}N_4O_5S[M+H]^+$ 375.1696, found 375.1701.

4-(4-Methoxybenzyl)-1-oxa-9-azaspiro[5.5]undecane-9-sulfonamide (1c)

Yield 138 mg, (39 %), white solid, m.p. 102-103 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.07 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.63 (s, 2H), 3.71 (s, 2H), 3.64 – 3.54 (m, 1H), 3.44 (t, *J* = 11.3 Hz, 1H), 3.35 (s, 2H), 3.12 (d, *J* = 8.4 Hz, 1H), 2.86 (td, *J* = 11.4, 3.3 Hz, 1H), 2.65 (t, *J* = 10.7 Hz, 1H), 2.39 (qd, *J* = 13.5, 7.1 Hz, 1H), 2.25 (d, *J* = 13.0 Hz, 1H), 1.87 (s, 1H), 1.62 – 1.37 (m, 2H), 1.22 (dt, *J* = 22.0, 5.9 Hz, 1H), 1.14 – 0.89 (m, 1H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.42, 131.41, 129.80, 113.53, 68.17, 60.02, 54.87, 41.77, 38.86, 38.77, 35.14, 31.92, 31.36, 25.28; HRMS (ESI), m/z calcd for $C_{17}H_{27}N_2O_4S[M+H]^+$ 355.1688, found 355.1686.

***N*-[9-(Aminosulfonyl)-1-oxa-9-azaspiro[5.5]undec-4-yl]-*N*-cyclopropylbenzamide (1d)**

Yield 162 mg, (41 %), white solid, m.p. 97-98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 – 7.30 (m, 5H), 6.68 (s, 2H), 4.35 (dd, *J* = 14.0, 8.9 Hz, 1H), 3.76 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.61 (dd, *J* = 22.0, 11.0 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.16 (t, *J* = 9.7 Hz, 2H), 2.90 (td, *J* = 11.0, 3.4 Hz, 1H), 2.70 (dd, *J* = 13.7, 7.6 Hz, 2H), 2.30 (d, *J* = 14.1 Hz, 1H), 2.12 – 1.94 (m, 1H), 1.92 – 1.73 (m, 3H), 1.71 – 1.53 (m, 2H), 1.43 (t, *J* = 11.2 Hz, 1H), 0.50 (d, *J* = 5.0 Hz, 2H), 0.34 (s, 2H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.76, 138.23, 129.24, 127.81, 127.11, 69.64, 60.14, 50.96, 38.86, 35.23, 30.28, 28.65, 25.30, 9.68, 9.55.; HRMS (ESI), m/z calcd for $C_{19}H_{28}N_3O_4S[M+H]^+$ 394.1795, found 394.1798.

4-(Morpholin-4-yl)-1-oxa-9-azaspiro[5.5]undecane-9-sulfonamide hydrochloride (1e·HCl)

Yield 175 mg, (49 %), white solid, m.p. 142-143 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 6.70 (s, 2H), 4.04 – 3.92 (m, 2H), 3.90 – 3.76 (m, 3H), 3.53 (dd, *J* = 20.9, 9.1 Hz, 2H), 3.47 – 3.27 (m, 7H), 3.25 – 3.12 (m, 2H), 3.11 – 2.93 (m, 2H), 2.87 (dd, *J* = 11.7, 8.6 Hz, 1H), 2.66 (t, *J* = 10.8 Hz, 1H), 2.21 (d, *J* = 13.6 Hz, 1H), 2.03 (t, *J* = 12.6 Hz, 2H), 1.75 – 1.47 (m, 4H), 1.40 (dd, *J* = 19.3, 7.0 Hz, 1H).; ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 70.24, 69.95, 63.99, 59.38, 48.86, 39.43, 39.27, 35.46, 34.70, 26.46, 25.56; HRMS (ESI), m/z calcd for $C_{13}H_{26}N_3O_4S[M+H]^+$ 320.1638, found 320.1641.

***N*-[9-(Aminosulfonyl)-1-oxa-9-azaspiro[5.5]undec-4-yl]-*N*-cyclopropylacetamide (1f)**

Yield 112 mg, (34 %), white solid, m.p. 75-76 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 6.66 (s, 2H), 4.25 (s, 1H), 3.69 (dd, *J* = 11.8, 4.4 Hz, 1H), 3.53 (dt, *J* = 23.4, 7.8 Hz, 2H), 3.13 (t, *J* = 12.2 Hz, 2H), 2.87 (td, *J* = 11.1, 3.8 Hz, 1H), 2.69 (dd, *J* = 11.6, 9.5 Hz, 1H), 2.57 (s, 1H), 2.27 (t, *J* = 12.4 Hz, 1H), 2.08 (s, 3H), 1.95 (qd, *J* = 12.2, 5.1 Hz, 1H), 1.79 (t, *J* = 12.7 Hz, 1H), 1.59 (dt, *J* = 25.3, 8.9 Hz, 4H), 1.47 – 1.30 (m, 1H), 0.93 – 0.64 (m, 4H).; ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 173.19, 69.77, 60.41, 50.44, 39.80, 39.11, 38.96, 35.36, 30.46, 28.72, 25.45, 23.85, 9.16.; HRMS (ESI), m/z calcd for $C_{14}H_{26}N_3O_4S[M+H]^+$ 332.1638, found 332.1639.

2-[9-(Aminosulfonyl)-1-oxa-9-azaspiro[5.5]undec-4-yl]-*N*-methylacetamide (1g)

Yield 166 mg, (55 %), white solid, m.p. 94-95 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.72 (d, *J* = 4.2 Hz, 1H), 6.65 (s, 2H), 3.61 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.47 (dd, *J* = 25.2, 13.4 Hz, 2H), 3.13 (t, *J* = 11.5 Hz, 2H), 2.99 – 2.76 (m, 1H), 2.67 (t, *J* = 10.7 Hz, 1H), 2.55 (d, *J* = 4.5 Hz, 3H), 2.35 – 2.19 (m, 1H), 2.07 (d, *J* = 11.1 Hz, 1H), 1.92 (d, *J* = 6.8 Hz, 2H).; ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 171.14, 68.20, 66.35, 60.01, 42.60, 41.71, 38.80, 35.14, 31.91, 27.10, 25.35, 25.32; HRMS (ESI), m/z calcd for $C_{12}H_{24}N_3O_4S[M+H]^+$ 306.1420, found 306.1422.

4-(Pyridin-4-yloxy)-1-oxa-9-azaspiro[5.5]undecane-9-sulfonamide hydrochloride (1h·HCl**)**

Yield 147 mg, (40 %), white solid, m.p. 138-139 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.74 (d, *J* = 7.0 Hz, 2H), 7.61 (d, *J* = 7.1 Hz, 2H), 6.70 (s, 2H), 5.29 – 5.08 (m, 1H), 3.81 (dd, *J* = 7.9, 4.2 Hz, 1H), 3.69 (t, *J* = 10.2 Hz, 1H), 3.17 (t, *J* = 10.1 Hz, 2H), 2.85 (dd, *J* = 11.7, 9.2 Hz, 1H), 2.74 (t, *J* = 10.7 Hz, 1H), 2.22 (d, *J* = 13.5 Hz, 1H), 2.10 – 1.94 (m, 2H), 1.78 (d, *J* = 12.2 Hz, 1H), 1.68 – 1.47 (m, 4H).; ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 162.96, 151.02, 111.08, 71.73, 69.62, 57.65, 41.47, 41.29, 40.58, 32.07, 31.59; HRMS (ESI), m/z calcd for $C_{14}H_{22}N_3O_4S[M+H]^+$ 328.1325, found 328.1329.

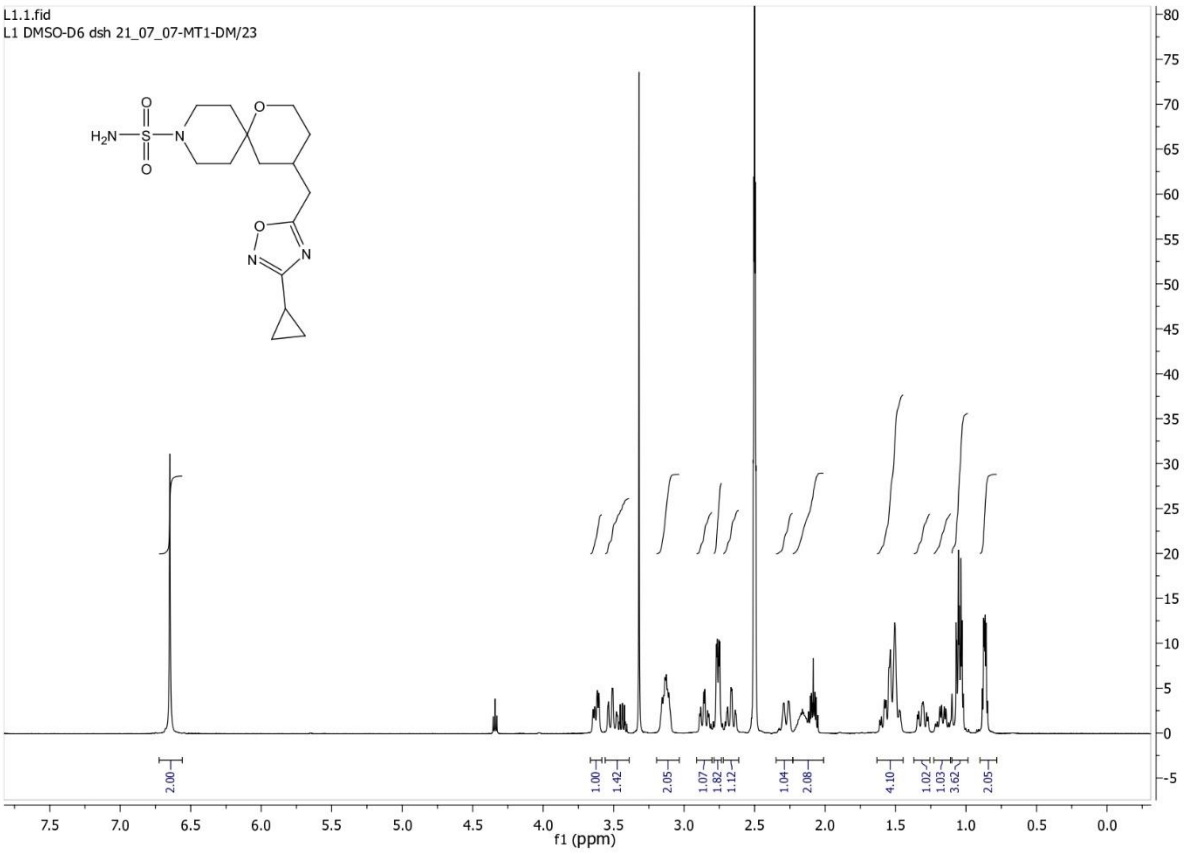
4-Ethoxy-1-oxa-9-azaspiro[5.5]undecane-9-sulfonamide (1i)

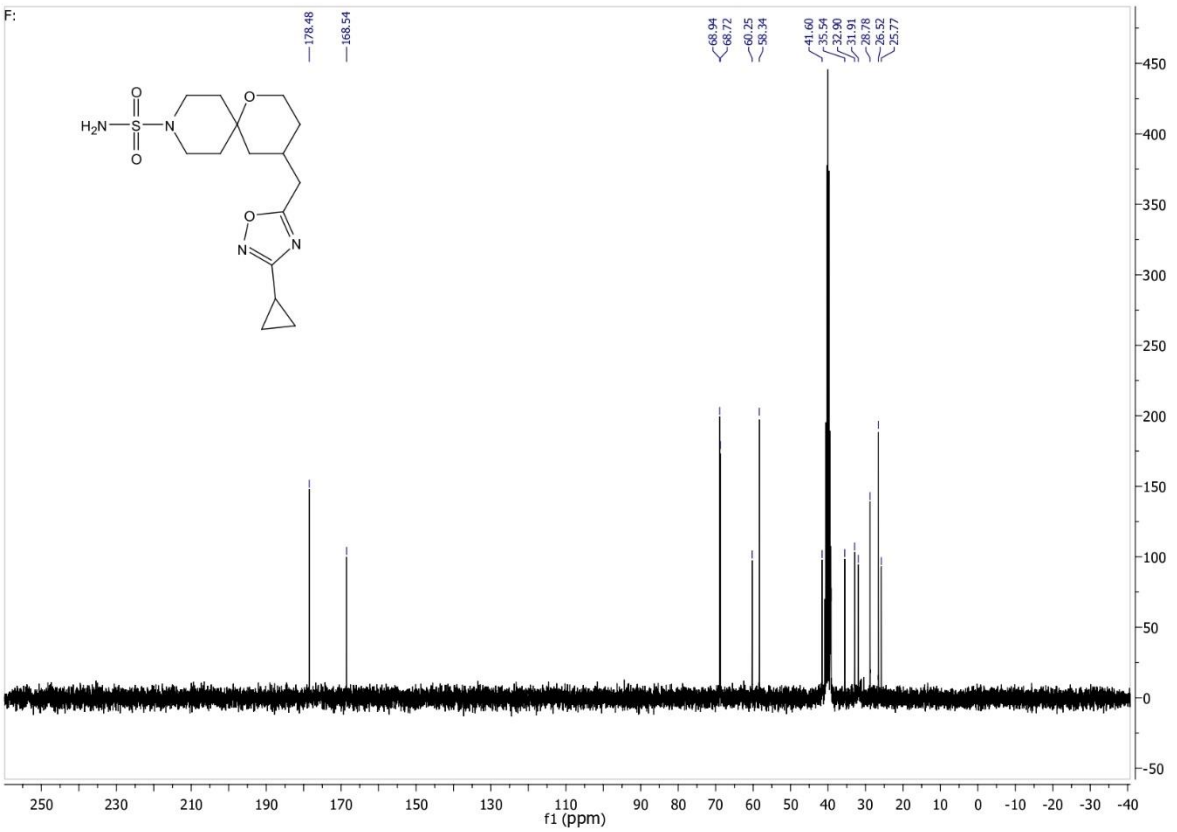
Yield 98 mg, (35 %), white solid, m.p. 78-79 °C; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 6.65 (s, 2H), 3.70 (dt, *J* = 11.8, 4.2 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.45 (qdd, *J* = 12.1, 10.6, 3.3 Hz, 5H), 3.12 (d, *J* = 11.4 Hz, 2H), 2.83 (td, *J* = 11.6, 2.9 Hz, 1H), 2.69 (dd, *J* = 11.7, 9.4 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.89 – 1.74 (m, 2H), 1.73 – 1.64 (m, 1H), 1.64 – 1.53 (m, 1H), 1.49 – 1.38 (m, 1H), 1.35 – 1.13 (m, 2H), 1.09 (dd, *J* = 11.6, 4.6 Hz, 3H).; ^{13}C NMR (75 MHz, DMSO-*d6*) δ 70.20, 69.13, 62.17, 58.41, 40.91, 38.79, 33.54, 31.93, 27.95, 15.55; HRMS (ESI), m/z calcd for $C_{11}H_{23}N_2O_4S[M+H]^+$ 279.1373, found 279.1376.

1-Oxa-9-azaspiro[5.5]undecane-9-sulfonamide (1j)

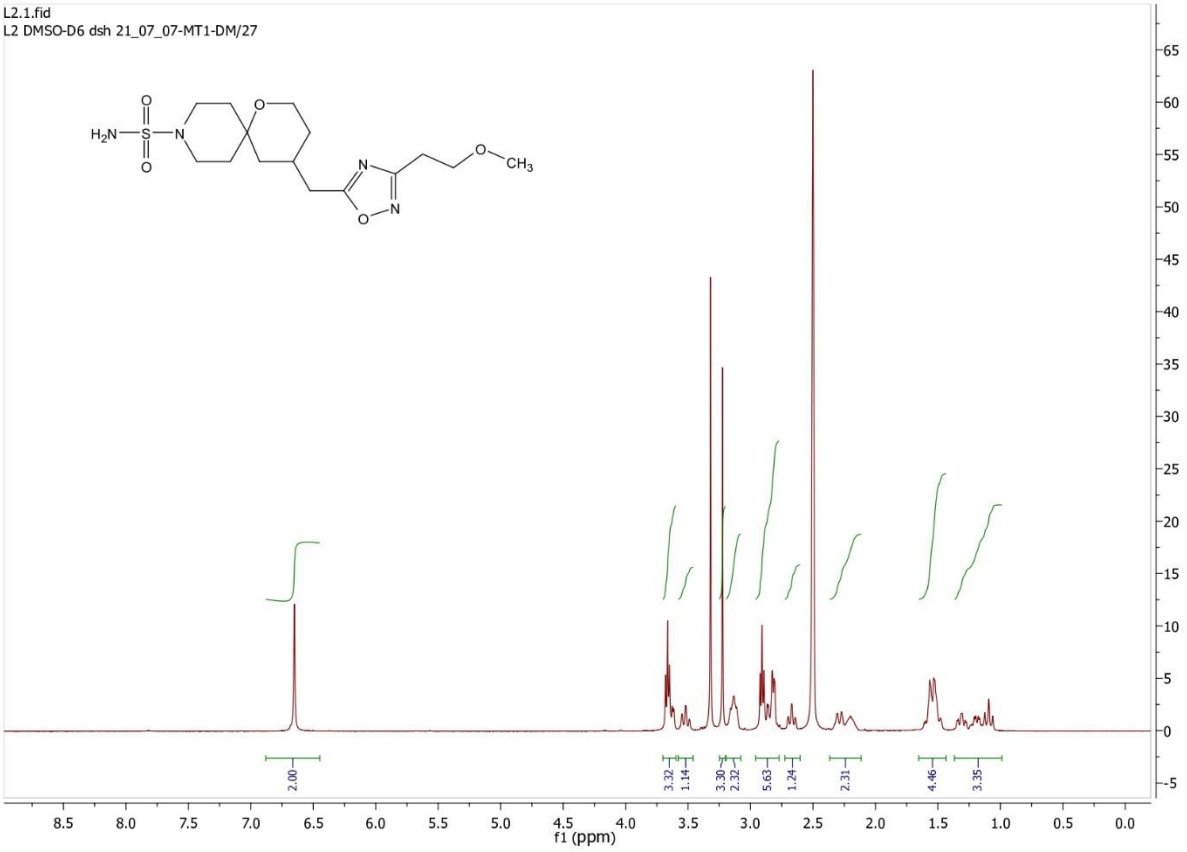
Yield 105 mg, (45 %), white solid, m.p. 106-107 °C; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 6.64 (s, 2H), 3.59 – 3.46 (m, 3H), 3.39 (s, 2H), 3.18 – 3.07 (m, 2H), 2.77 (td, *J* = 11.7, 2.5 Hz, 2H), 1.91 (d, *J* = 12.7 Hz, 2H), 1.57 (dt, *J* = 11.9, 5.9 Hz, 2H), 1.49 – 1.29 (m, 7H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 68.38, 66.41, 59.89, 41.47, 35.32, 32.68, 25.73, 18.36.; HRMS (ESI), m/z calcd for $C_9H_{19}N_2O_3S[M+H]^+$ 235.1111, found 235.1114.

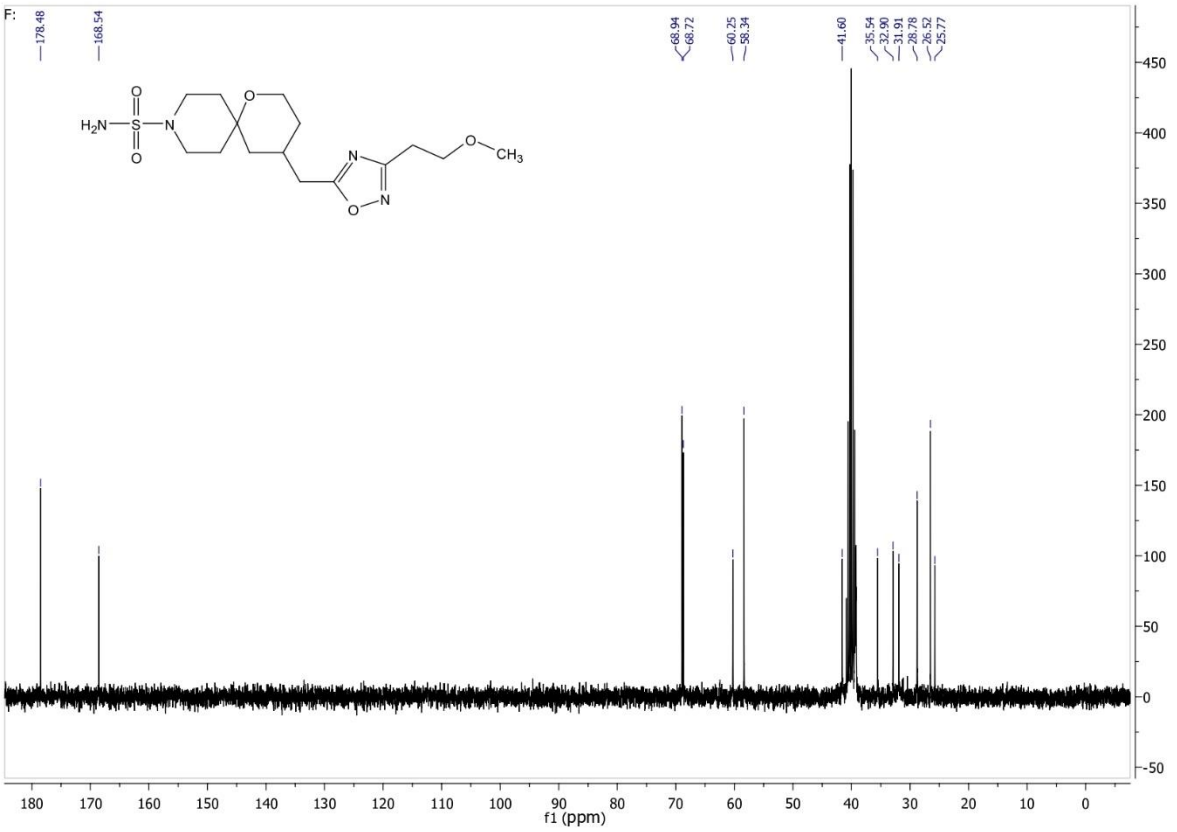
Copies of ^{1}H and ^{13}C NMR spectra of compound **4a**





Copies of ^{1}H and ^{13}C NMR spectra of compound **4b**





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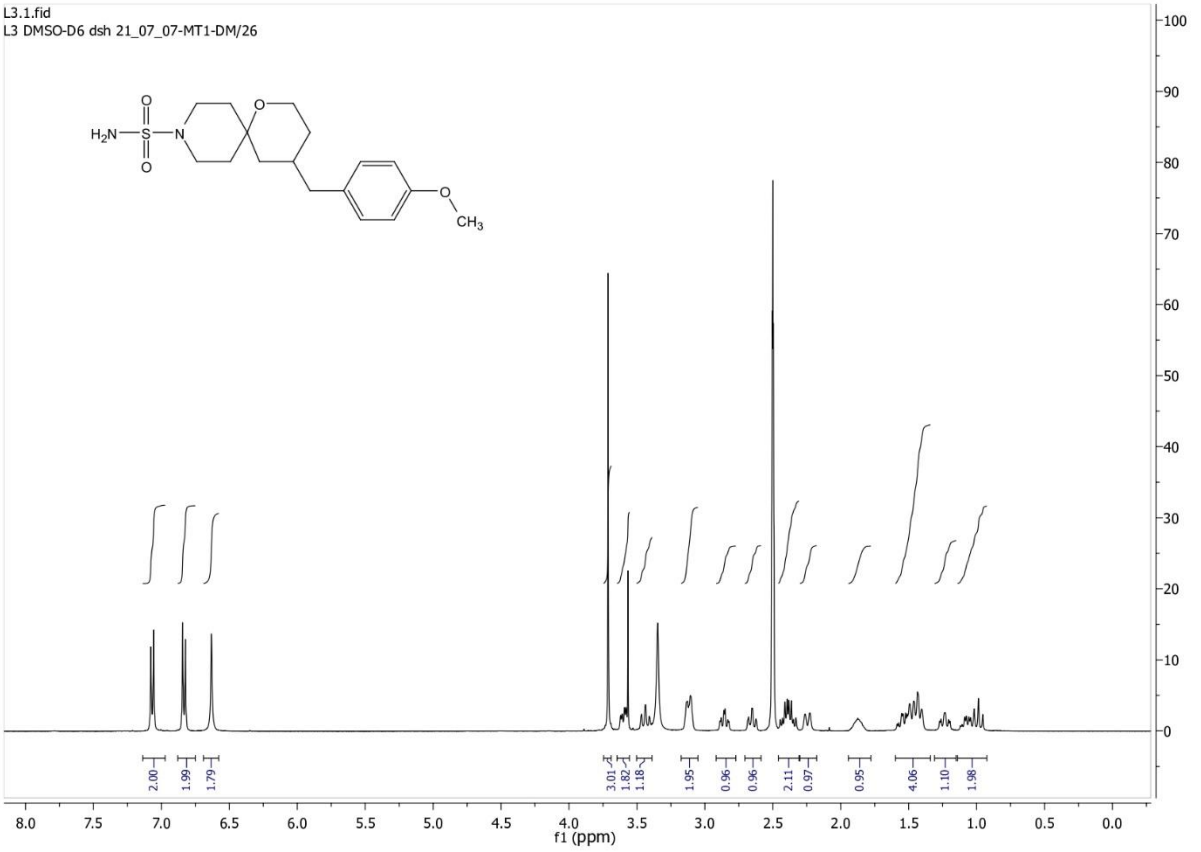

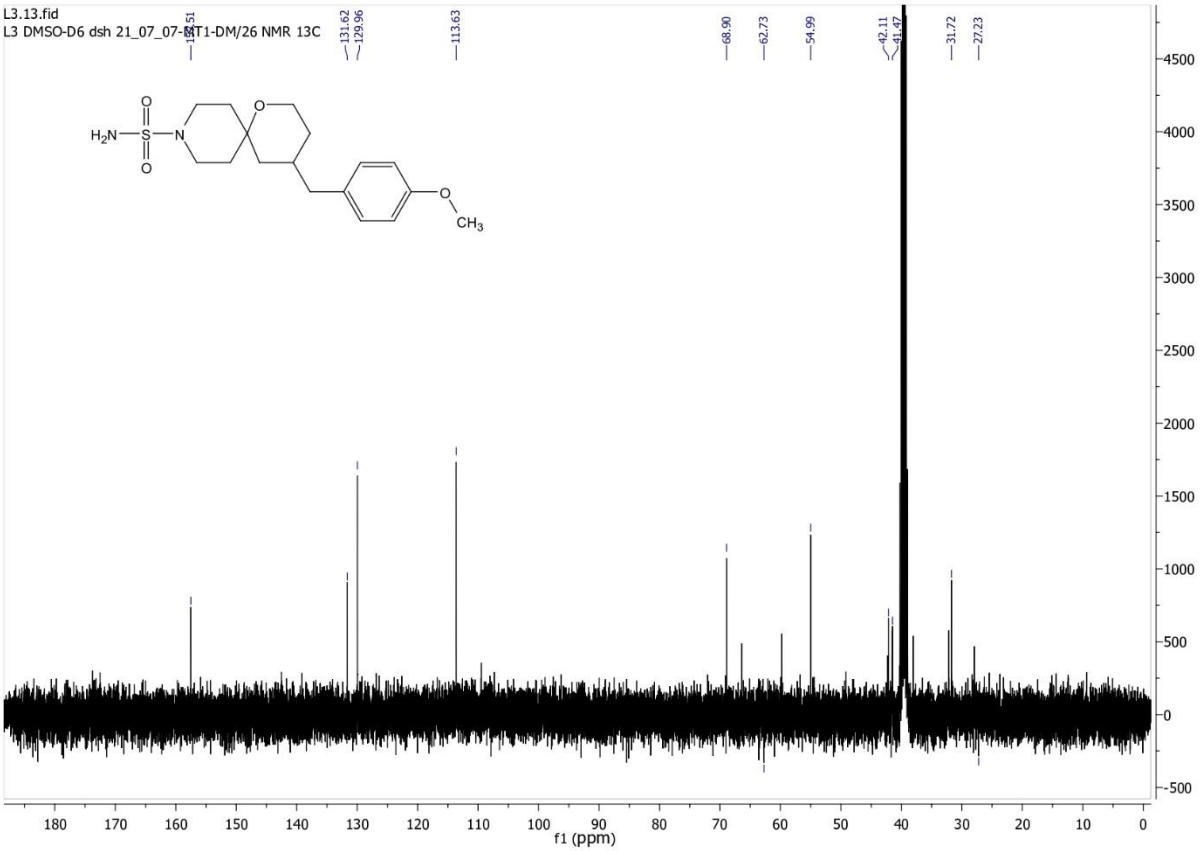

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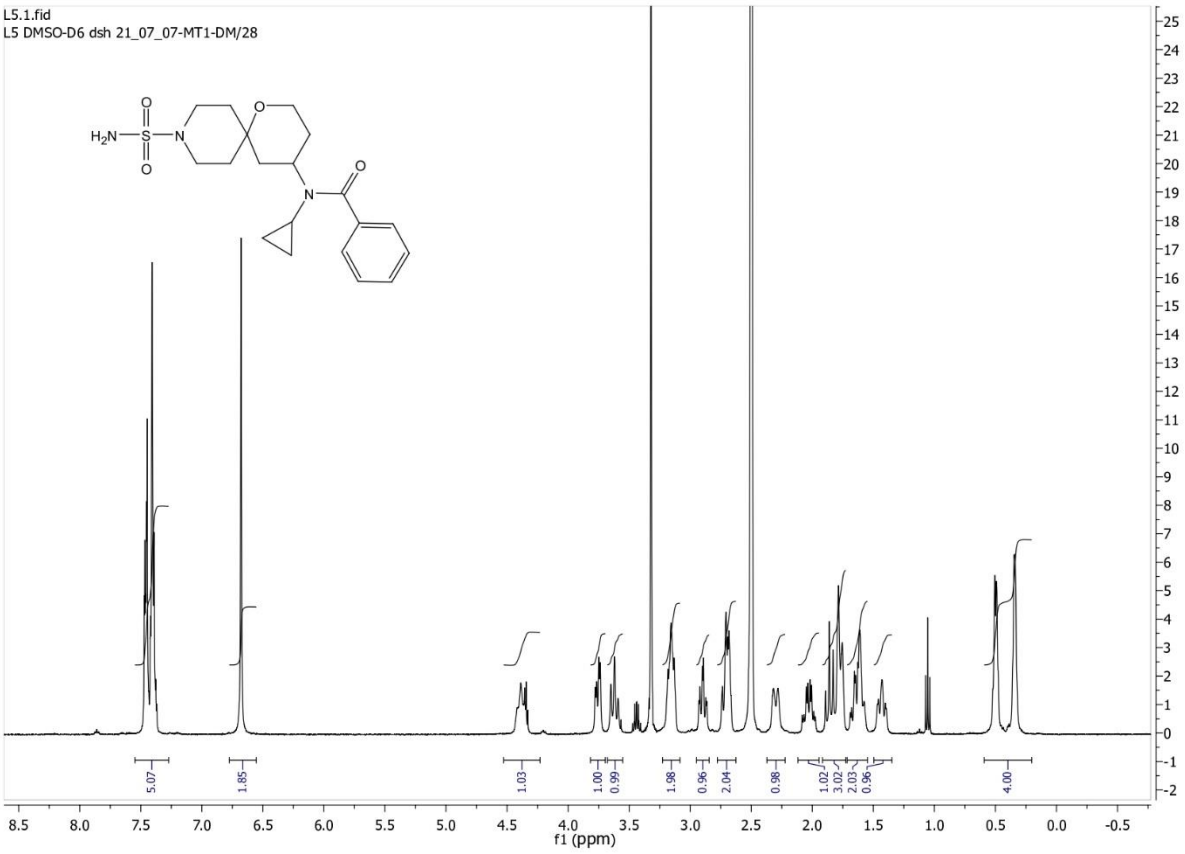

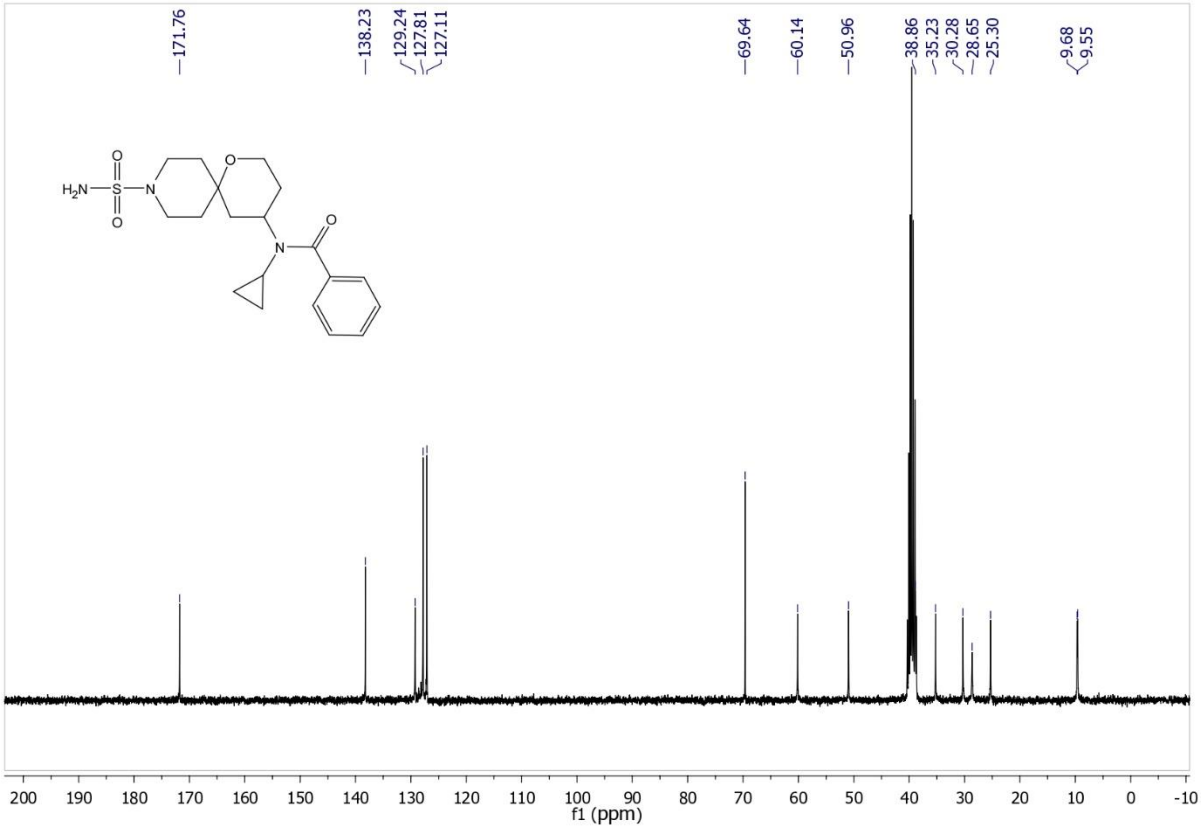

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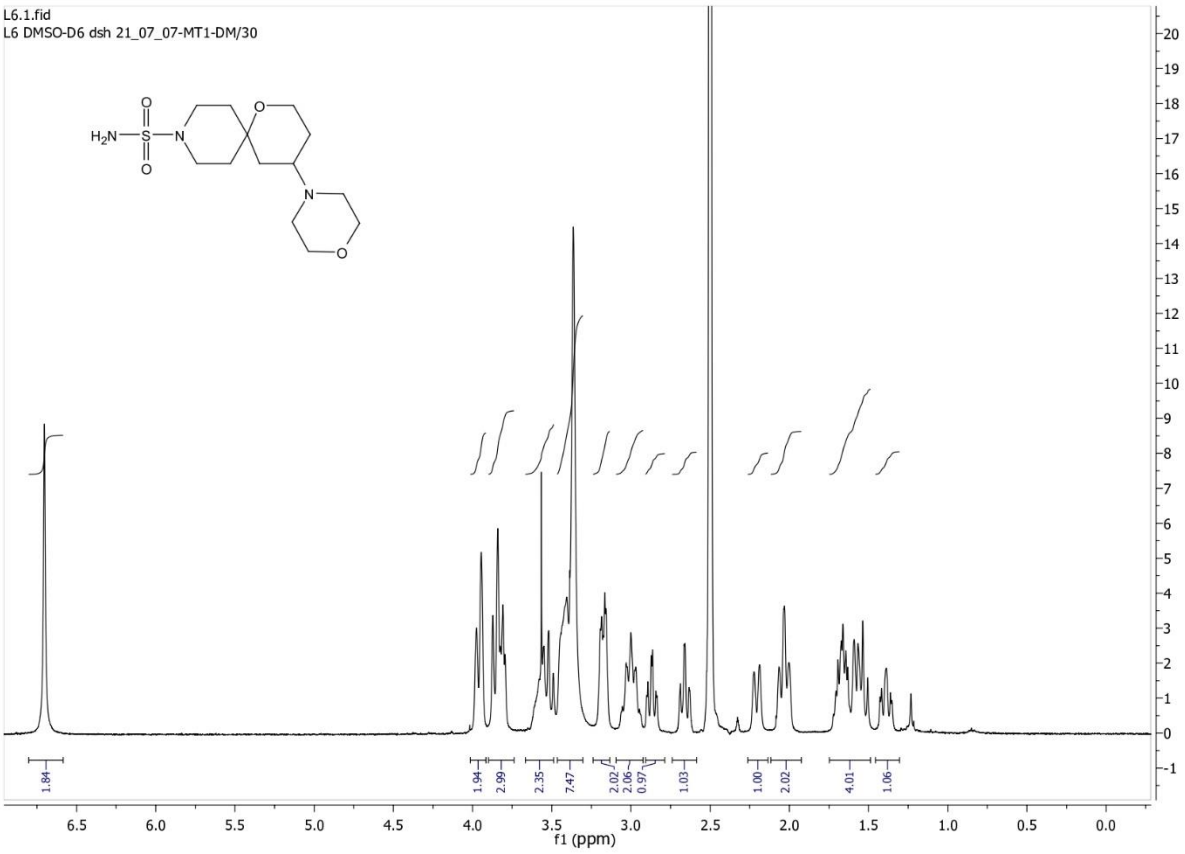
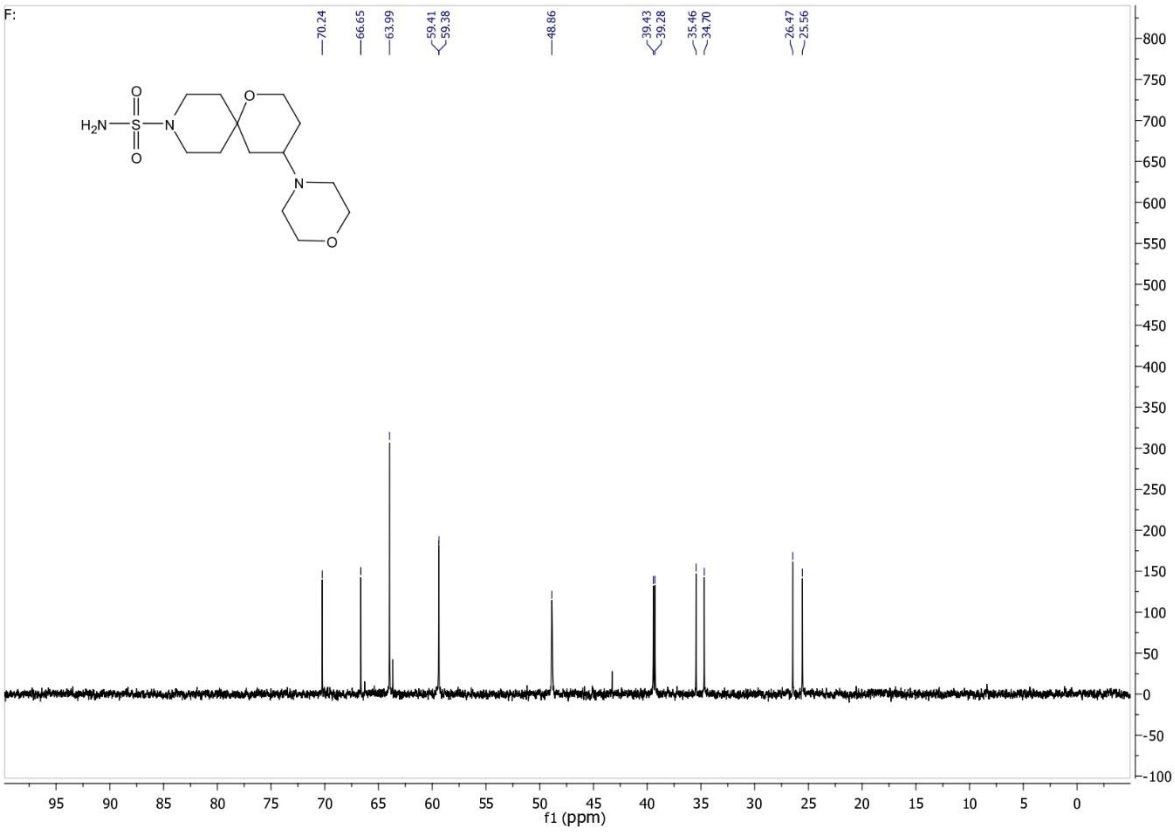
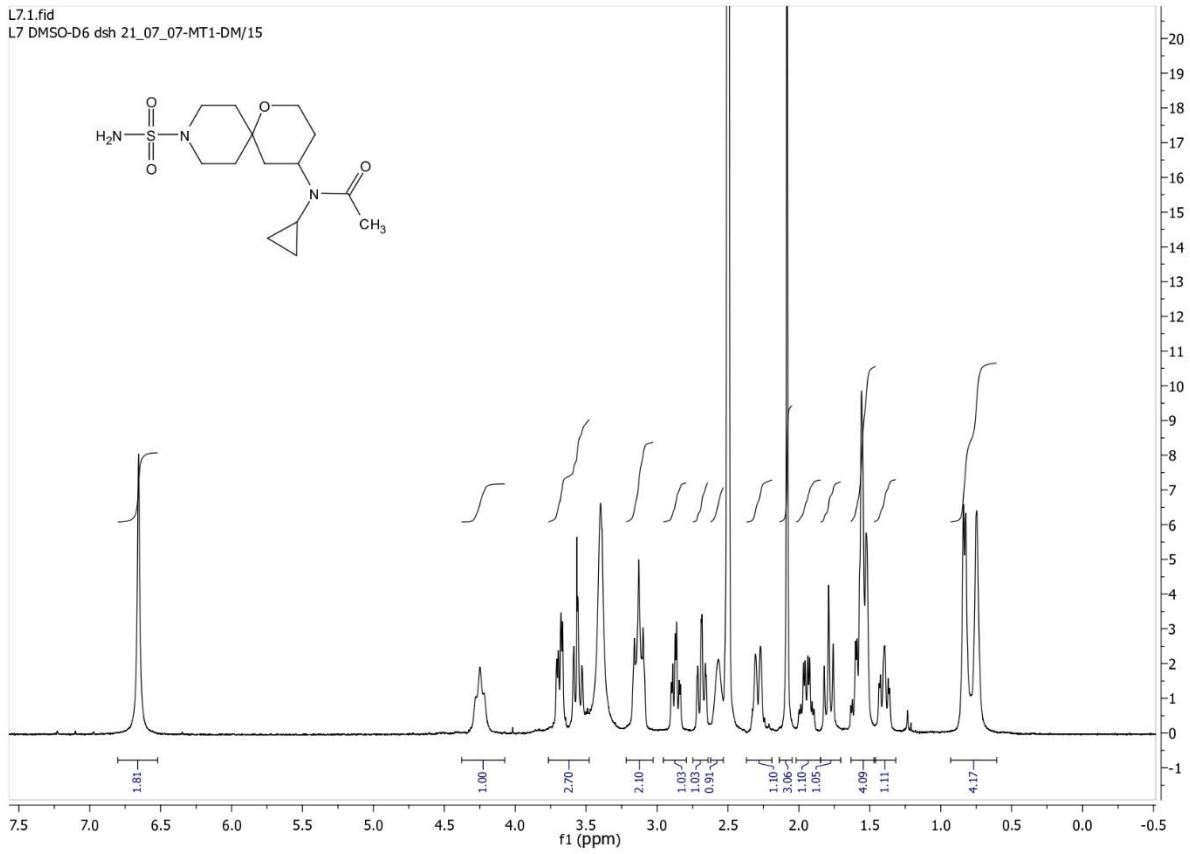
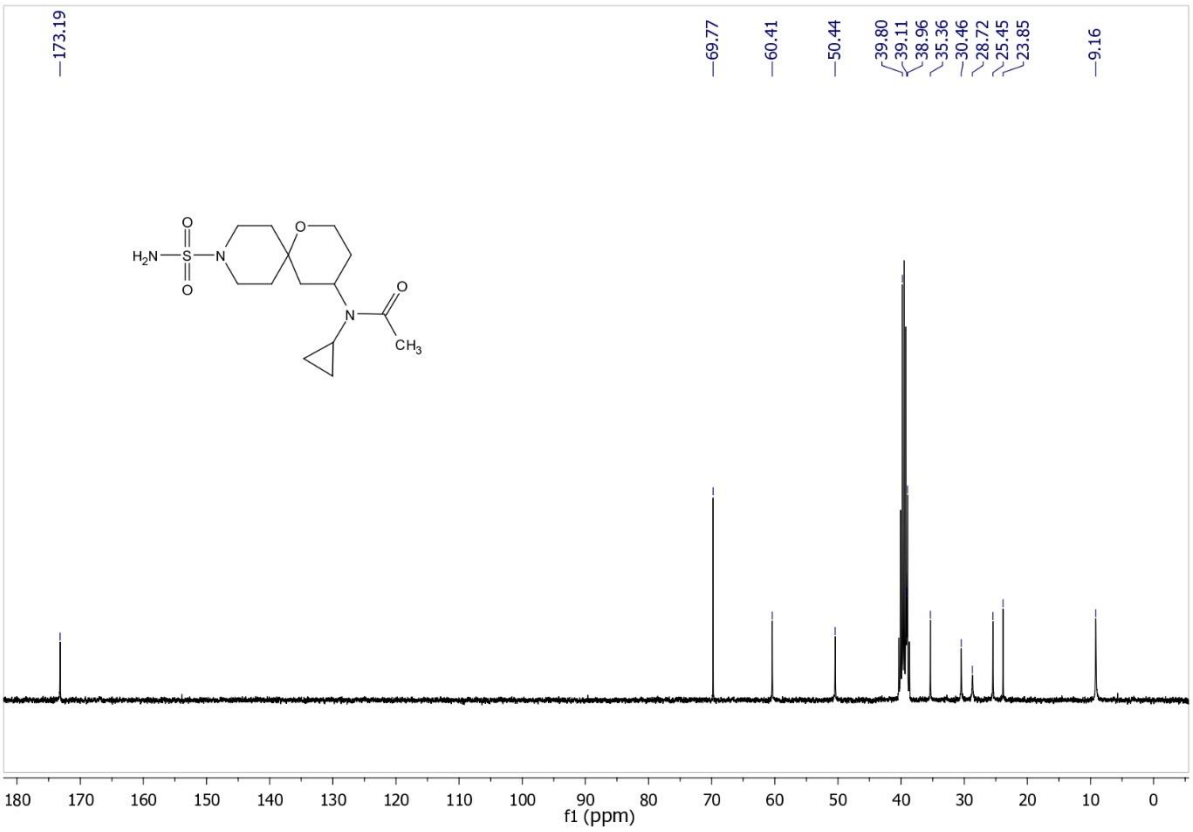


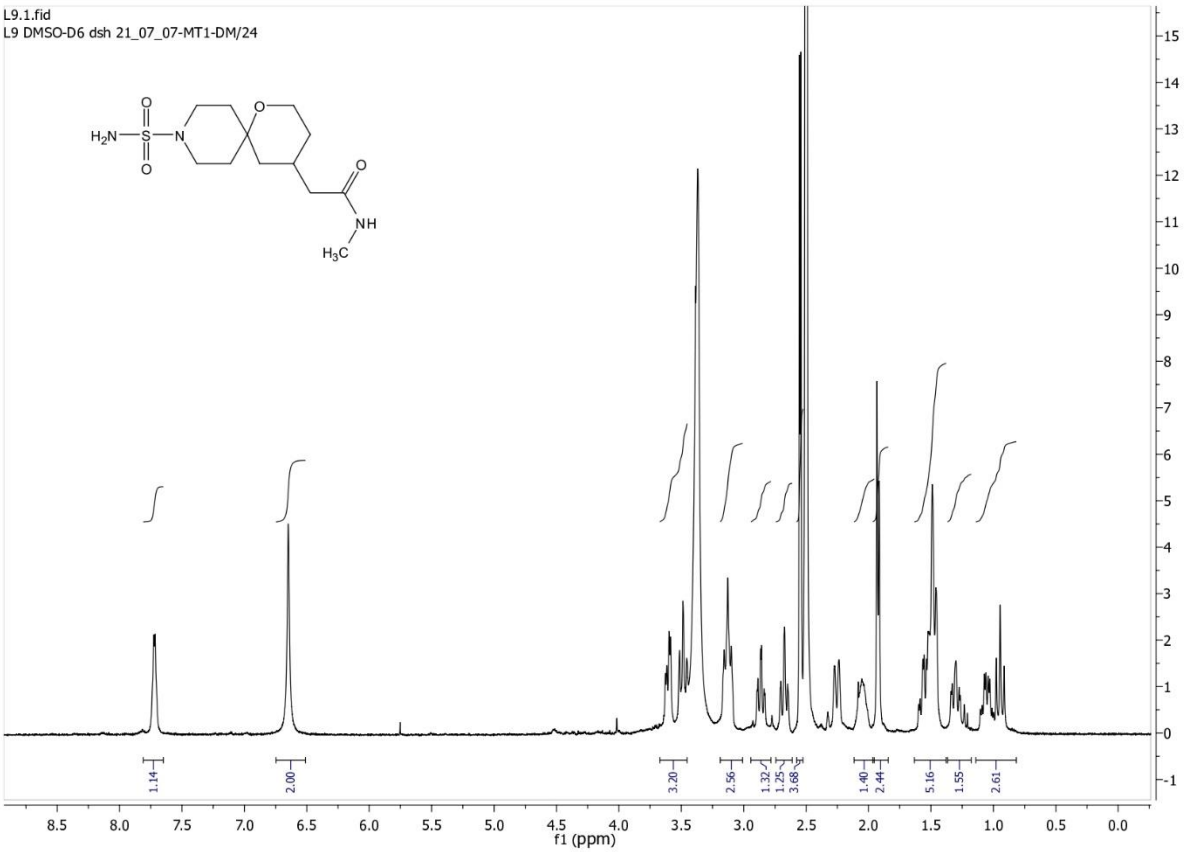


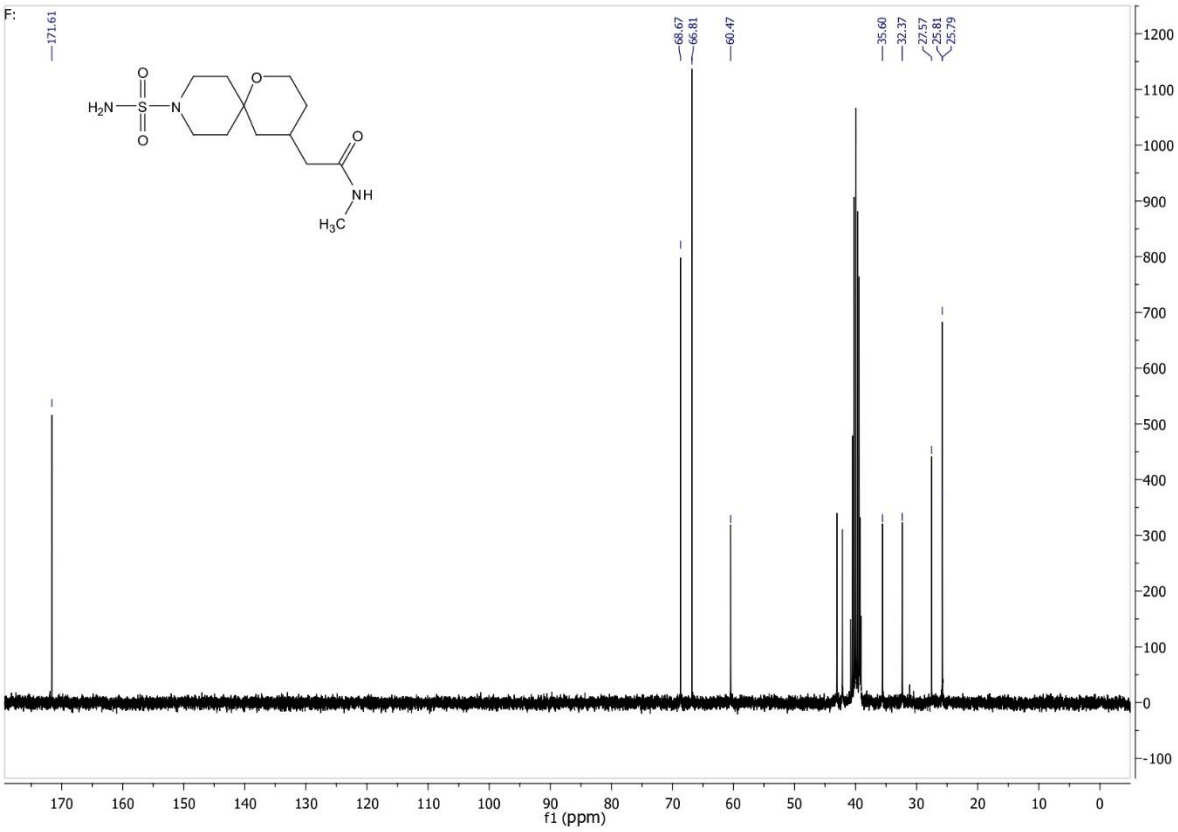
Copies of ^{1}H and ^{13}C NMR spectra of compound **4f**



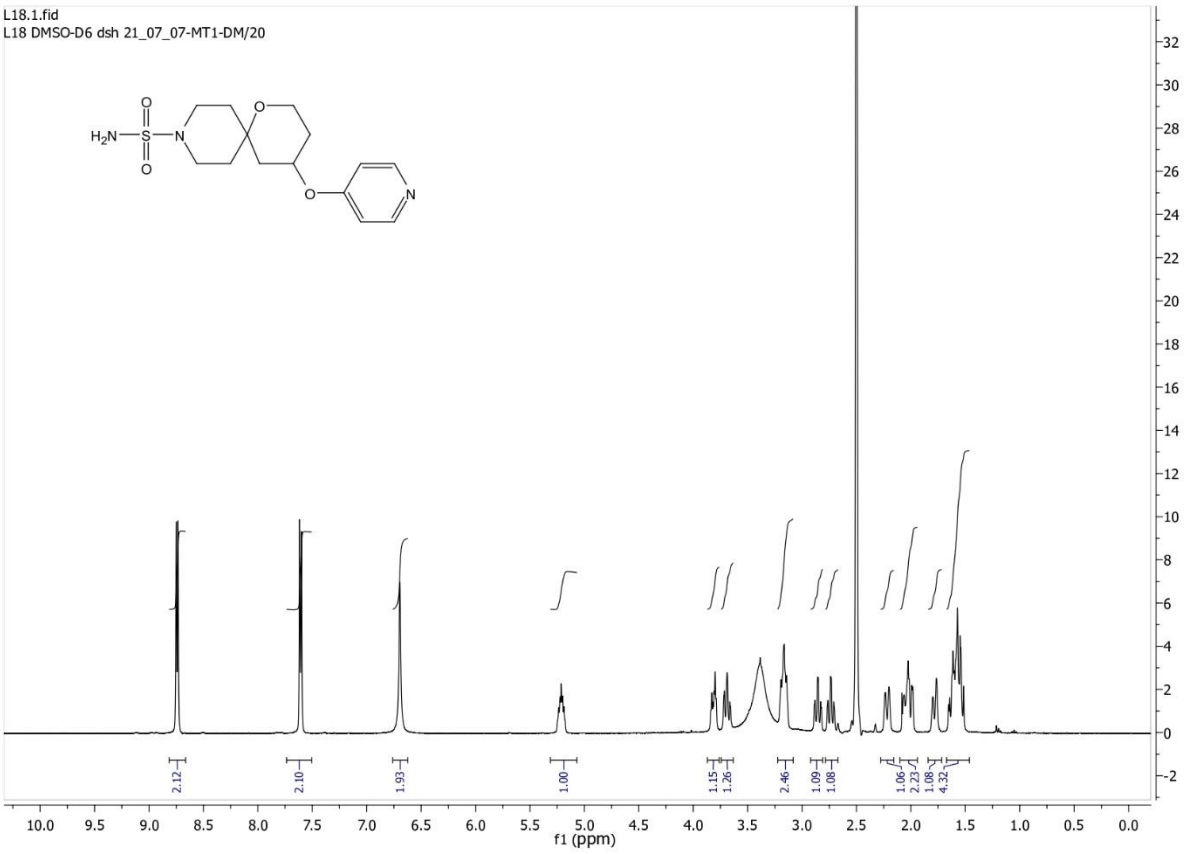


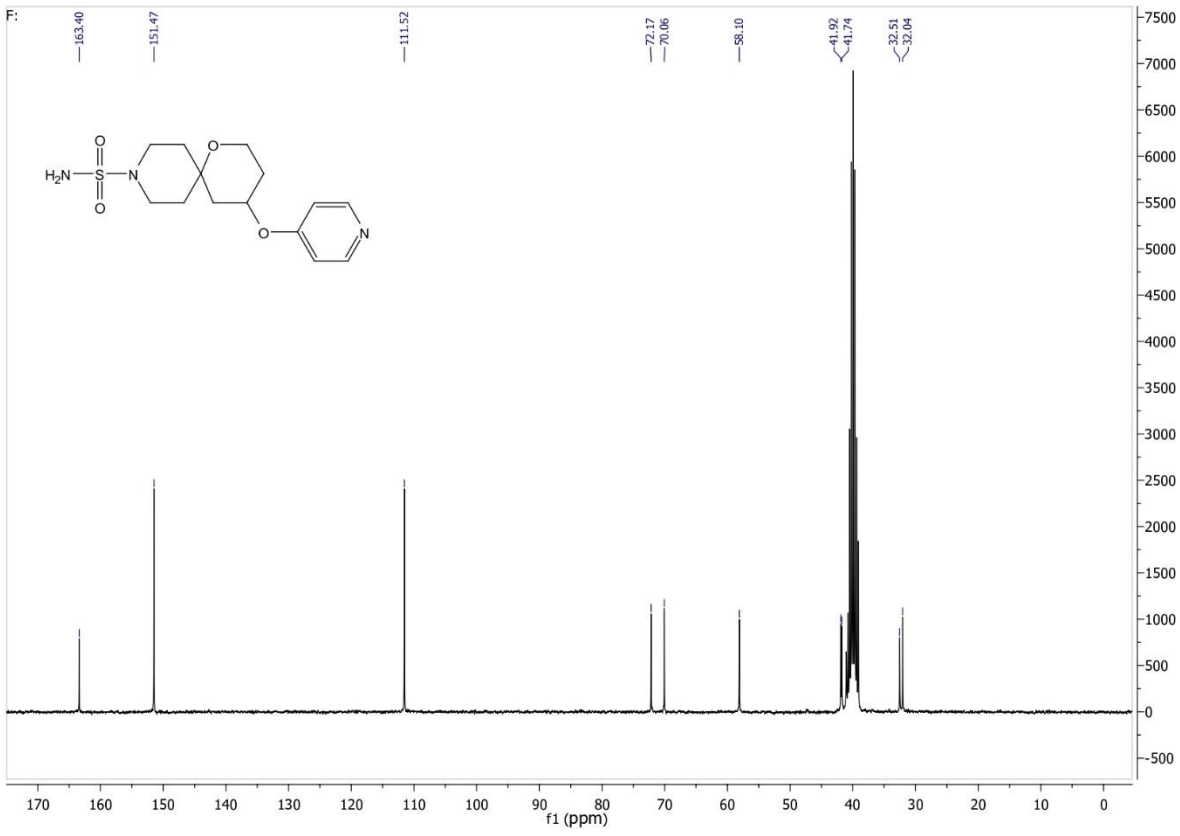
Copies of ^{1}H and ^{13}C NMR spectra of compound **4g**



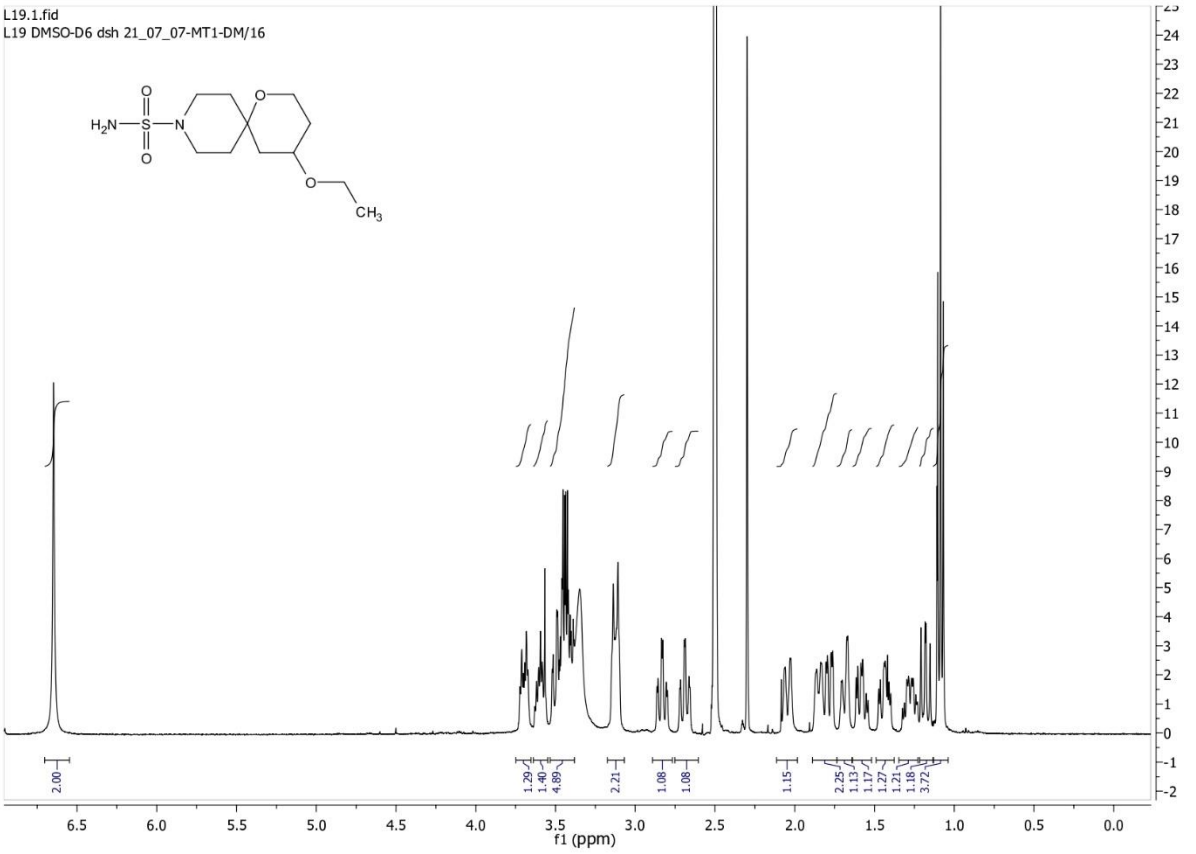


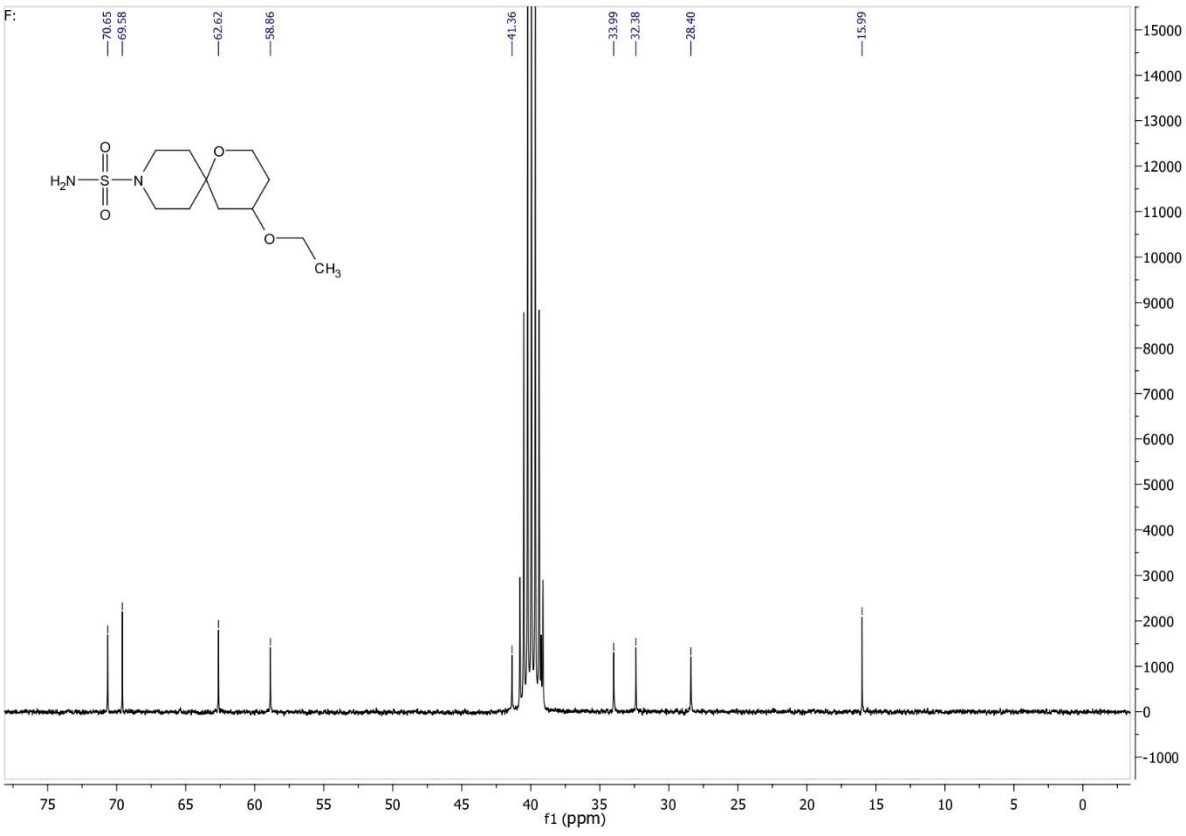
Copies of ^{1}H and ^{13}C NMR spectra of compound **4h**·HCl





Copies of ^{1}H and ^{13}C NMR spectra of compound **4i**





Copies of ^{1}H and ^{13}C NMR spectra of compound **4j**